Dreams and Realities in Disease Eradication
Fogarty Lecture
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For those in public health and epidemiology, the concept of totally eradicating a disease has long been a siren song. Jenner himself is often credited with first envisaging such a goal. **(SLIDE)** The statement by Jenner was essentially an expression of buoyant optimism as he sought to persuade early skeptics of the importance of vaccination. Certainly, he did not foresee a global program. **(SLIDE)** Important impetus to the concept of disease eradication was provided by the respected Charles Chapin who stated that "any disease that can be prevented in part, can be prevented in its entirety." (SLIDE) This belief was eventually taken seriously by a number of prominent public health advocates, the most notable and charismatic being Dr. Fred Soper. This manifested itself in six global eradication campaigns.**(SLIDE)**

Eradication, in its proper sense, represents the ultimate achievement in preventive medicine. It implies that, with eradication, preventive measures may cease with all that that implies with regard to savings. Cost-benefit analyses extending out to infinity promise to provide returns on investment that challenge belief. It is not surprising that, for some, the promise of eliminating a disease, once and for all, has transcended reason and the campaigns themselves have sometimes assumed the characteristics of a crusade, not readily challenged by practical experience or reality. Accounts of both the yellow fever and malaria programs portray this vividly.

The fact, however, is that only one disease has been successfully eradicated; four others have failed; and two that are currently being pursued, are encountering heavy weather. As we move into the 21st Century, what is the reality? What might be our eradication agenda?

Interest, indeed belief, in eradication virtually collapsed during the mid to late 1960's. This was the result of the aggressively promoted and costly global malaria eradication effort faltering and finally collapsing. More than $2 billion was eventually expended before it was finally accepted that the tools for the task were inadequate. In 1965, the great Rene Dubos eloquently expressed what was a widespread perception. **(SLIDE)** Indeed, when smallpox eradication was proposed to the World Health

Assembly only one year later, many opposed launching yet another eradication effort and UNICEF, which had so generously supported the malaria program, stated at the Assembly that it would make no money available for smallpox eradication or any other eradication campaign. For smallpox, UNICEF kept its promise and provided no support.

The success of smallpox eradication rekindled the dying embers of interest in eradication. And, so it was, in 1980, only a month after the pronouncement at the World Health Assembly that eradication had been achieved, an international meeting was convened at Stone House to explore the question of what diseases should next be eradicated. To most of us who had just celebrated the eradication of smallpox, the discussions were all but incomprehensible. Although the smallpox epidemiologists had been a large, diverse and talented group, I didn't recall the question of what next to eradicate ever having been seriously discussed. Why? It was clear to all of us that despite all the attributes of smallpox that favored eradication as well as having an ideal vaccine, the achievement had been a narrow victory, the likelihood having been in doubt only months before the conclusion. No other disease came close in terms of attributes favorable to eradication. But the Fogarty meeting, as it turned out was but the first of a series of eradication conferences. At that first meeting, a surprising number of diseases and conditions were nominated and solemnly contemplated. These ranged from urban rabies to periodontal disease to leprosy. (**SLIDE**) Ultimately, it was decided that measles, polio and yaws were most suitable but that there were many other possible candidates for at least regional eradication.

Frank Fenner and I, as keynote speakers at the meeting apparently expressed sufficient unwanted skepticism that we were never again invited as keynote speakers, if indeed we were invited at all, to the many eradication conferences that followed.

As we celebrate the 35th Anniversary of Fogarty's lecture series and the 23rd year since the inaugural eradication conference, it is appropriate that we revisit the question of the future of eradication. Today, there are two global eradication campaigns that have been agreed upon in the World Health Assembly and are in progress– one for polio and one for Guinea Worm disease. The polio program has truly been a global effort; that for Guinea Worm is no less important but it is, more properly, a regional program that bas involved only a limited number of countries in tropical Africa and Asia.

The decision to launch polio eradication in 1988 had been in recognition of the fact that the prospects for eradication of that disease were brighter than for any other disease and this was reaffirmed at the IOM Forum in 2001 that dealt with Viral Disease Eradication. At that Forum, two other candidate diseases for eradication were discussed in detail –measles and rubella. **(SLIDE)** It was acknowledged, however, that both posed significant epidemiological and technical challenges that made the prospects for eradication of those diseases substantially less likely than for polio. Given these considerations, I will restrict my observations today to the polio eradication effort because it has been generally agreed that until polio had been successfully eradicated, it would be undesirable to launch another eradication effort. Today, I should like to review briefly the status of that program and what eradication might imply. This is important because a number of epidemiological assumptions about the virus and the disease have changed over time as well as, more recently, assumptions about projected savings that might accrue from eradication. These need to be recognized as the eradication program enters what is hoped to be its final stages.

The polio program is now concluding its 14th year. **(SLIDE)** Its primary goal had been the achievement of eradication by the year 2000, later revised to 2002 and later to 2005. A new target is to be expected because the declaration of eradication requires that 3 years of surveillance elapse during which no cases are found. The program has enjoyed unprecedented support from countries around the world as well as from private entities, including, notably, Rotary International. Expenditures are approaching $2 billion. Dedicated staff in all countries have labored diligently and with dedication. **(SLIDE)** Landmarks of progress include the interruption of transmission throughout 3 WHO Regions as well as in a number of other African and Asian countries. **(SLIDE)** During 2002, known reported cases will probably number somewhat over 2000 when final reports are received. Only 6 countries are known to have had cases in 2002 but, unfortunately, these include 3 of the world's largest and most densely populated–Nigeria, Pakistan and India. Additional foci may be found when it is possible to conduct adequate surveillance programs in countries such as Congo, southern Sudan, and Angola. It is clear that although much has been done, there remains a great deal to do.

Following eradication, it had been expected that vaccination and other control measures could cease. The resulting savings are projected to be substantial enough to offset, within a few years, the additional expenditures that have been required to conduct an eradication campaign, a significantly more costly effort than one for disease control. This, it was thought, would parallel the experience with smallpox eradication, vaccination having ceased in the early 1980s along with vaccine production and a number of control measures such as quarantine inspectors to examine vaccination certificates. However, during the past two years, the wisdom of that course of action has been questioned. As you know, there is now the realistic fear that terrorists might resort to the use of smallpox as a weapon and, what with a now highly susceptible population both in this and other countries the potential for catastrophic spread of smallpox now exists. Many countries are now restarting vaccine production and are stocking vaccine; diagnostic laboratories are being set up; and other measures are being taken to strengthen surveillance and international coordination. In some countries, the vaccination of health care staff is taking place.

In brief, it is now apparent that although global eradication of a *disease* might be possible, certainty regarding eradication of the virus itself will never be possible. Rene Dubos was prescient. Therefore, plans have to be made to anticipate the possible reemergence of any virus whose human to human transmission is thought to have been interrupted. For smallpox, I believe it is possible that, if we had a reasonably safe vaccine, we might well resume a universal vaccination program, much as what we have today for diphtheria, tetanus, measles, rubella and several other diseases. Such would apply to polio as well were transmission to be interrupted.

Thus, it is obvious that whatever projected savings in vaccination and control programs were once anticipated as a result of eradication now have to be substantially discounted from projected cost-benefit equations. The fact that stopping vaccination is not an option has yet to be accepted but I will return to this subject later.

Why should the polio program be proving so much more costly and so much more difficult that was smallpox. The extraordinary differences between these two diseases in terms of their epidemiology and the tools available are not appreciated by most. In

contemplating the possibility of eradicating a disease posing even more difficult challenges – and all of them do – this needs to be kept in mind.

(SLIDES I , II, III, IV,VI,VII)

Simply identifying the laboratories that might have polio is a mind-numbing exercise **(SLIDE)** A concerted global effort was made by WHO to identify all laboratories that might have strains of smallpox virus -- of some 823 identified virology laboratories, 75 indicated that they had strains of the virus. The Organization was spurred on by repeated demands from many recently endemic countries to take action to request that all laboratories destroy their stocks or transfer them to a WHO Reference Laboratory. I would note, was not readily achieved. It took a great deal of persuasion and considerable political arm twisting. By 1983, all had given formal assurances to WHO that they had done so.

Would that it had been possible to confirm this but, realistically, an effort to search REVCO's and other freezers across the world for tiny ampoules possibly containing smallpox virus was simply not feasible. Bottom line, however, is that there were probably very few laboratories indeed by 1983 that retained smallpox virus.

Beginning in 1990, a U.S.-led initiative proposed that the remaining stocks of smallpox virus be destroyed. A WHO expert committee determined that, so far as was known, no research utilizing variola virus had been conducted for nearly 10 years and none were able to identify a possible use for the virus. To preserve genetic information, the Committee arranged for cloned libraries of smallpox virus to be preserved and, later, supported an initiative to map the genomes of representative strains. Meanwhile, five major professional organizations, specifically solicited as to their views about destroying the smallpox virus, all agreed that this was a desirable action to take. However, in 1996, on the eve of a decision by the WHO Executive Board to recommend destruction of the virus, the U.S. reversed its position, insisting that it was crucial to retain smallpox virus indefinitely to permit research studies on antiviral compounds and new vaccines. These

studies were essential, it was said, because no one could say where smallpox virus might still reside or whether someone might, at some time release the virus.

Whether right or wrong, this decision implicitly introduced a new dimension into the question of the policies and programs that would need to be in place after the natural circulation of any virus had been confirmed

These considerations pertain with equal force to the polio virus. But first, the question has to be asked as to when polio itself can be eradicated. The time table is shifting and there seems to be no obvious way to deal with the two must recently discovered problems that I highlighted.

But even if polio is eradicated, what difference will it make? Look to the smallpox experience and recognize that eternal vigilance will be mandatory and that vaccination will need to continue, perhaps forever, unless we are prepared to mount a population wide revaccination program should the disease reemerge. To counter epidemic polio again would require enormous quantities of OPV to contain it. Note that one can't contain polio like one can smallpox. Is any country prepared to pay the costs to store hundreds of millions of doses of OPV, if indeed long-term storage is possible, in fact? Is someone prepared to pay the costs of sustaining a very large manufacturing capability for the indefinite future? Why are we not now reshaping the polio program, as it is apparent we must, to provide for a long-term vaccination effort, just as we now deal with other vaccine preventable diseases. The World Health Assembly, I would note, voted to support a program for the eradication of polio, not for the eradication of oral poliovaccine.

Why is it important to critically examine the eradication issues? Eradication programs are far more costly than those for control. With concerns about national security, with a growing recognition that new and emerging diseases are of more than academic concern, I believe we must seriously ask the questions "What are our highest priorities?" "What are the most critical disease challenges that should be able to be controlled and what research is needed to determine how best to do this?"

My candidates for an enhanced effort are measles, HIV/AIDS, TB and Malaria – not one of these would I propose be a candidate for eradication.

We should, instead, decide now to eradicate one thing – the word, "eradication".**(SLIDE)**

Dreams and Realities in Disease Eradication

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"It now becomes too manifest to admit of controversy, that the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practice."

Edward Jenner, 1801

"Any disease that can be prevented in part, can be prevented in its entirety."

Charles Chapin, 1888

Six Global Eradication Campaigns

Disease	Method	Duration	Years
*Yellow Fever	Vector control	1915-32	17
Yaws	Penicillin	1948-66	18
Malaria	DDT	1955-73	18
*Smallpox	Vaccine	1967-80	13
Guinea Worm	Water: Rx	1986-	16+
*Poliomyelitis	Vaccine	1988-	14+

*Viral disease eradication

Reflections on Eradication

"Eradication involves a new biological philosophy. It implies that it is possible and desirable to get rid of certain disease problems by eliminating completely the etiological agents, once and for all.... Social considerations, in fact, make it probably useless to discuss the theoretical flaws and technical difficulties of eradication programs, because more earthy factors will certainly bring them soon to a gentle and silent death...eradication programs will eventually become a curiosity item on library shelves, just as have all social utopias."

Man Adapting, by Dr. Rene Dubos (1965)

Fogarty Conference -- 1980

- Candidates for global eradication
  - Measles
  - Polio
  - Yaws
- Candidates for regional eradication
  - Many

IOM Forum -- 2001

- Candidates for virus eradication
  Polio -- in progress
- Possible but much more difficult
  - Measles
  - Rubella

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Polio eradication targets

- Program launched in 1988--
  Projected occurrence of last case
  - 2000 (original target)
  - 2002 (revised in 1999)
  - 2005 (revised in 2002)
  - 2005+ (due for revision)

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Status - Polio Eradication 2002

- Eradication achieved in 3 Regions
  - Americas
  - Europe
  - Western Pacific

  Not yet achieved in 3 Regions
  - Africa
  - Southeast Asia
  - Eastern Mediterranean

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Polio Cases – 2002

- Reported and confirmed
  - India – 1509 Nigeria – 174
    Pakistan – 90 Afghanistan – 9
    Niger - 3 Egypt - 5

Uncertain – surveillance pending
Democratic Republic of the Congo
Angola, Sudan

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Key Attributes in Smallpox Epidemiology

- Surveillance-Containment
  - Visible rash – all cases
  - Readily diagnosed
  - Minimal demand for lab
  - Targeted containment
- Epidemiology
  - Transmission only by clinical cases
  - No long-term carriers
  - Moderately contagious

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Comparison of Key Attributes of Smallpox and Polio Epidemiology

Smallpox	Polio
Surveillance-Containment	
Visible rash – all cases	1/200 with paralysis
Readily diagnosed	Flaccid paralysis problem
Minimal demand for lab	Heavy lab demand
Targeted containment	Areawide campaigns
Epidemiology	
Transmission only by cases	Primarily by asymptomatic
Moderately contagious	More contagious

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Key Attributes of Smallpox Vaccine

- Vaccine
  - Heat stable
  - Production in endemic countries
  - One dose
  - Protects against all strains
  - No reversion to virulence
  - Easily stored for 45+ years

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Key Attributes of Smallpox and Polio Vaccines

Smallpox	Polio
Heat stable	Labile
Production in endemic countries	No
One dose	5+ OPV: 4+ IPV
Protects-all strains	3 vaccine strains
Easily stored for 45+ years	c. 5 years

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Two Critical Poliovaccine Problems

Unknown in 1988

- Poliovaccine virus can be excreted for 10+ years
  - One well studied case:
    - Excretion in high titer
    - Virulent in monkeys
    - Resistant to antiviral therapies
- Poliovaccine virus can revert to virulence
  - Can Cause outbreaks of paralytic disease
    - Egypt, Haiti, Madagascar, Philippines, Dominican Republic
  - Silent Spread for 2 to ? years

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Confining the Virus Sources for Reemergence

- Polio diagnostic and research laboratories
- Other laboratories with stool specimens
- Areas where surveillance is limited or impossible
- IPV production laboratories
- Revertent OPV Polio Strains
- Long Term OPV Carriers
- Biological weapons laboratories

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Smallpox Eradication: Laboratories Retaining Smallpox Virus

	No. of	No. retaining smallpox		
Region	Labs	1975	1977	1983
Americas	506	18	13	1
Europe	185	29	19	1
Africa	15	5	4	0
Southeast Asia	57	13	13	0
Eastern Med.	25	3	3	0
West. Pacific	35	7	5	0
TOTAL	823	75	57	2

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What next do we eradicate?

What are the most critical disease challenges that should be able to be controlled?

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